Remarks

Claims 1-19 were present in the application as filed. By preliminary amendment filed with the initial application papers, claim 6 was canceled and claim 20 was added, thereby resulting in pending claims 1-5 and 7-20. Claims 1-5 were amended in a paper that was filed contemporaneously with the filing of a Request for Continued Examination under 37 C.F.R. §1.114 to remove the finality of a final Office Action mailed July 7, 2003. Claims 18 and 20 are canceled above. Claims 1-5 and 7-17 and 19 remain pending in the application.

Claim 1 is amended herein to more clearly define the claimed method. Accordingly, claim 1 recites a method comprising treating a pharmaceutical drug or vaccine with a concentration of an ionic surfactant that is effective to dissociate the endotoxin from the amphiphilic pharmaceutical drug or vaccine *without affecting the ability of the pharmaceutical drug or vaccine to be retained by a molecular weight cut-off filter having a pore size effective to retain the amphiphilic pharmaceutical drug or vaccine substance but allow the disassociated bacterial endotoxin to pass therethrough.* Directly after treatment with the ionic surfactant, the solution is filtered through the molecular weight cut-off filter. Claim 1 is further amended to incorporate the feature of claim 18, that is, to include a further process step of removing surfactant from the process solution whereby the amount of ionic surfactant remaining in said solution *is less than 0.002%.*

Support for the amendments are found in the specification on page 6, second full paragraph and page 17, first full paragraph.

Claim Rejection Under 35 USC §112, first paragraph

The Advisory Action dated April 4, 2005 contains a new matter rejection of the claims under 35 U.S.C.§112, first paragraph. The Office Action states that the claim language "without adversely affecting the properties of the drug or vaccine including its ability to be retained by a filter..." does not appear in the specification, or original claims as filed. In fact, the language at issue appears in the specification on page 6, second full paragraph. Claim 1 is amended above to reflect the desired effect of the surfactant in the claimed method using similar terminology.

With respect to the further amendment of claim 1 above, particularly with respect to the amount of ionic surfactant remaining in the solution after a further surfactant removal step being less that 0.02%, support for the amendment is found in the specification on page 17, first full paragraph.

Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim Rejection Under 35 USC §103(a)

Claims 1-5 and 7-20 remain rejected as being unpatentable over Shanbrom (EP 0 083 999) in view of Shanbrom (U.S. Patent 4,315,919). In view of the above amendments, Applicants' believe that the combination of Shanbrom (EP 0 083 999) and Shanbrom (U.S. Patent 4,315,919) does not teach the claimed invention.

Applicants' invention provides a method of removing bacterial endotoxin from an amphiphilic pharmaceutical drug or vaccine. Some amphiphilic vaccines, such as protein antigens, present special challenges with respect to endotoxin removal since 1) the antigens and endotoxin become strongly associated under aqueous conditions due to both having amphiphilic structures, and 2) the native conformation of the antigen must be preserved.

For viral protein antigens such as influenza virus hemagglutinin (HA), which occur in complexes called "rosettes", maintenance of the quarternary structure of the antigen is important and the challenge is to dissociate the endotoxin from the drug or vaccine without affecting this attribute of the drug or vaccine.

Applicants' solution to this problem is to treat the process solution with an *ionic*, preferably anionic surfactant, which is able to dissociate the endotoxin from the amphiphilic drug or vaccine substance without altering the structure of the drug or vaccine itself. Inherent in the trimeric structure of influenza HA antigen rosettes, for example, is its molecular weight and concomitantly, its ability to be retained by the MWCO filter. The resulting solution is then subjected to ultrafiltration such that the larger amphiphilic drug or vaccine complex is retained by the filter, while the smaller, dissociated endotoxin fragments and surfactant pass through the filter.

Additionally, removal of the surfactant following treatment is an important step because it is not desirable in the end product and it interferes with the determination of endotoxin in the sample. Accordingly, the process solution is subjected to a further process step in which the surfactant is removed to less than 0.002%.

The depyrogenation method taught by Shanbrom ('919) purports to using a non-denaturing amphiphile, including reference to ionic and non-ionic surfactants, in conjunction with protein precipitation methods to remove endotoxin from biological and pharmaceutical products. The reference, however, only provides evidence with respect to the **non-ionic** surfactant, Triton-X 100 (See Examples 1-5). Significantly, Shanbrom ('919) additionally contains a disclaimer with respect to the use of some *ionic* surfactants, for example as sodium deoxycholate. Based on this negative teaching with respect to an ionic surfactant and the lack of examples illustrating the feasibility of using any other ionic surfactant, it is likely that one of skill would conclude that the use of ionic surfactants is not warranted.

Shanbrom (EP) teaches depyrogenation of an aqueous albumin solution using a **non-ionic** surfactant followed by filtration with a 10kd MWCO filter. Given the inconclusive teachings of the '919 patent, Applicant contends that one of skill would not be motivated to combine the references in the first place and that even the combination does not teach Applicants' claimed method. Therefore, Applicants' method can not be obvious over Shanbrom ('919) in view of Shanbrom (EP).

Furthermore, neither Shanbrom reference discusses the level of residual surfactant remaining in the final product.

As previously discussed, therefore, the deficiencies of Shanbrom ('919) are not cured by the addition of the teachings of Shanbrom (EP), since neither reference actually teaches the feasibility of removing endotoxin from an amphiphilic substance using an ionic surfactant without compromising its molecular structure or the removal of surfactant to a level below 0.002%. Without such teachings, the claims as amended herein, cannot be obvious.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. The dependent claims are believed allowable for the same reasons as the independent claims from which they ultimately depend, as well as for their additional limitations. Should the Examiner require clarification of any of the above, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Kathy Smith Dias
Attorney for Applicants
Registration Number 41,707
HESLIN ROTHENBERG FARLEY & MESITI P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579